REMARKS

Claims 78-100 are pending in the subject application. Applicants have hereinabove canceled claim 94 without disclaimer or prejudice to their right to pursue the subject matter of this claim in a later-filed application and amended claims 78, 93 and 95-97 and 99. Support for these amendments may be found inter alia in the specification as follows: page 12, lines 23-31. This amendment does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 78-93 and 95-100 will be pending.

Objection to the specification

The Examiner stated the prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No.9). The Examiner stated that applicants submit that they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner stated until applicants submit a proper Figure said objection is maintained.

In response, applicants will submit a new Figure 6B upon the indication of allowable subject matter.

Obviousness-type double patenting rejection

The Examiner provisionally rejected claims 78-100 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 78-115 of copending Application No. 08/477,097 for reasons previously made of record for claims, 53, 55-57 and 59-77. The Examiner stated that applicants assert that the added new claims in the copending application obviate the

obvious type double patenting. The Examiner stated Applicants' arguments are not persuasive since the instantly claimed GM2-KLH conjugate and methods anticipate the corresponding GM2-KLH conjugate and methods of use thereof in the copending 08/477,097 application. The Examiner stated Applicants amendments are insufficient to remove the rejection.

The Examiner provisionally rejected claims 78-100 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 46-56 of copending Application Nos. 08/477, 147 for reasons previously made of record for claims 53, 55-57 and 59-77. The Examiner stated that although the conflicting claims are not identical, they are not patently distinct from each other for the reasons set forth in the prior Office Actions. The Examiner stated the instant conjugate species of GM2, GM3, GD3, GD3 lactone, o-acetyl GD3. and GT3 and methods of use thereof anticipate the conjugates and methods of the 08/477,147 application, in as much as, the '154 application claims GM2-KLH conjugates and methods of use. The Examiner stated applicants' amendments are insufficient to overcome the double patenting rejection.

The Examiner provisionally rejected claims 78-100 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of application No 08/196,154 for reasons previously made of record for claims 53, 55-57 and 59-77. The Examiner stated that the instantly claimed composition drawn to the specific species of GM2 ganglioside conjugate to KLH, anticipates all the pending claims of 08/196,154, in as much as the '154 application claims GM2-KLH conjugates and

methods of use.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims of the cited applications do not render obvious the claims of the subject application and therefore, an obviousness-type double patenting rejection is not appropriate. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 78-81 and 83-100 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed October 6, 1999 (see Paper No. 20) for claims 53-57, 59-72 and new claims 73-77 and the Office Action mailed 10-5-99.

The Examiner stated as to claims 78-81 and 83-100, applicants' arguments' and amendments have been carefully considered. The Examiner stated that the claims still recite "derivatives of KLH". The Examiner stated such derivatives are not enabled for reasons already made of record. The Examiner stated that applicants' arguments and amendments are insufficient to obviate this rejection.

The Examiner stated that as to new claims 94-100, the claims are enabled for the use of the composition only for the treatment of

cancer but are not enabled for the prevention of cancer, for reasons made of record in Paper No. 8, mailed June 13, 1996. The Examiner stated that applicants' arguments have been carefully considered but are not persuasive. The Examiner stated that applicants' argue that the conjugate vaccine of the invention prevents outgrowth of micrometastases and prevents cancer per se (Zhang et al, Cancer Research 58:2844-2849, 1998). The Examiner stated this is not persuasive, the claims are not drawn to preventing outgrowth of micrometastases and the conjugate used in the paper is GD2-KLH (10 ug of GD2 conjugated to 60 ug KPH, wherein the conjugation of GD2 of KLH was achieved by conversion of the GD2 ceramide double bond to aldehyde by ozonolysis and attachment to KLH by reductive amination in the presence of cyanoborohydride) plus 10 ug QS-21. The Examiner stated thus, the conjugate of the claims is not that which has been demonstrated by the art to prevent outgrowth of micrometastases, nor does the method provide for the method of the paper (multiple doses administered by a specific route. Moreover, the article specifically teaches that the vaccine "...should be used exclusively in the adjuvant setting, where circulating tumor cells and micrometastases are the primary targets (page 2844, last line of abstract)." The Examiner stated the evidence of the paper targeted circulating cells specific type of tumor cell (lymphoma) which was administered intravenously and micrometastases thereof from circulation, which is clearly not representative of cancers or relapses as instantly claimed. The Examiner stated moreover, figure 1, demonstrates that administration of the GD2-KPH, QS-21 vaccine at days -21, -14 and -7 does not prevent cancer as demonstrated by the death of some of the experimental group after experimental intravenous challenge of lymphoma cells (see Figure 1, Experiments 3 and 6B). The Examiner

stated at page 2845, column 2, second and third paragraph, Zhang et al teach that the vaccine prolonged survival, but in the discussion of experiment 6, only 4 out of 6 vaccinated mice remained disease free at the latest time point measured. The Examiner stated moreover, Zhang et al admit that the alleged protection in Experiment 7 of Figure 1, was "not statistically significant" and moreover this experiment is not directly comparable with the other experiments because the tumor burden administered intravenously was substantially reduced. The Examiner stated clearly the vaccine when administered prior to the cancer does not prevent as claimed or as argued by applicant. The Examiner stated additionally, prevention of relapse as claimed has not been demonstrated nor specifically addressed by this paper and Zhang et al admits that "If antibodies of sufficient titer and potency to eliminate circulating cancer cells and micrometastases could be maintained in cancer patients as well, even metastic cancer would have a quite different implication. The Examiner stated with continuing showers of metastases no longer possible, aggressive treatment of primary and metastic sites might result in long term control." The Examiner stated relapsing of cancer is quite different than elimination of micrometastases (see page 2848, column 1, last paragraph) not primary cancer. The Examiner stated Zhang et al do not address primary cancer and the experimental protocols set forth therein do not address prevention of primary cancer as is claimed for prevention of relapse of cancer. The Examiner stated reduction of circulating lymphoma cells and reduction in micrometastases is not commensurate in scope with prevention of cancer or prevention of a relapse of cancer.

In response, with respect to the Examiner's above rejection concerning KLH derivatives, applicants respectfully traverse the

Examiner's the rejection. Claims which recite "derivatives of KLH" are enabled. Applicants respectfully direct the Examiner's attention to page 12, lines 4-13 for examples of generating such derivatives. For example, one skilled in the art could generate a KLH derivative by directly liking it to an immunological adjuvant, such as monophospholipid A, non-ionic block copolymers or a cytokine, as taught by on page 12, lines 4-13 of the specification.

With respect to the Examiner's above rejection concerning the prevention of cancer, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein canceled claim 94 without disclaimer or prejudice to their right to pursue the subject matter of this claim in a later-filed application. In addition, applicants acknowledge the Examiner's statement that the claims are enabled for the use of the composition for the treatment. Accordingly, applicants have also hereinabove amended claim 95 such that it now recites a "method of treating a cancer in a subject." Therefore , the claimed invention is enabled.

Applicants contend that these amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 78-95 and 97-100 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al. (Seminars in Cancer Biology), Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol), Kensil et

al. (The Journal of Immunology), Marciani et al. (Vaccine) and Uemura et al (J Biochem) for reasons made of record for previous claims 18-20, 53, 55-67 and 69-72 in Paper No. 23, 10-5-99.

The Examiner stated that applicants' arguments have been carefully considered but are not persuasive. The Examiner stated that applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation of the ganglioside derivative through a ceramide derived carbon. The Examiner stated this is not persuasive, the conjugation procedure as combined provides for the identical procedure as Applicants' coupling procedure. The Examiner stated moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various shingolipids did not affect the haptenic reactivity with antibodies. The Examiner stated Applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the prior art would not arrived at the claimed product and methods. The Examiner stated Applicants arguments are not persuasive and the rejection stands across the new claims.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully disagree with the Examiner's contention that the conjugation procedure as combined provides for the identical procedure as applicants' coupling procedure. Applicants contend that the cited references, namely Livingston et al. (Cancer Research) in view of Ritter et al. (Seminars in Cancer Biology), Liane et al (Journal of Biological Chemistry), Livingston

et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol), Kensil et al. (The Journal of Immunology), and Marciani et al. (Vaccine) and Uemura et al (J Biochem) does not teach, suggest or disclose applicants claimed invention and therefore do not render obvious the claimed invention.

Applicants point out that newly amended claim 78 recites a "composition which comprises: a) a conjugate of i) a ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising a sphingosine base, to ii) Keyhole Limpet Hemocyanin or a derivative thereof comprising an ε-aminolysyl group; b) a saponin derivable from the bark of a Quillaja saponaria Molina tree; and c) a pharmaceutically acceptable carrier; the relative amounts of such conjugate and such saponin being effective to stimulate or enhance antibody production in a subject; wherein the ganglioside derivative is a derivative of a ganglioside selected from the group consisting of GM2, GM3, GD2, GD3, GD3 lactone, O-acetyl GD3 and GT3; and **wherein in the conjugate the ganglioside derivative is conjugated to Keyhole Limpet Hemocyanin or the derivative thereof through a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative to the ε-aminolysyl group of Keyhole Limpet Hemocyanin or the derivative thereof**" [emphasis added].

First, the Examiner acknowledges that the primary reference, i.e. Livingston et al. Cancer Research 1989, ("Livingston 1989") does not teach conjugation of GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on KLH in a composition or using this method for treatment (see October 5, 1999 Office Action, page 10).

To compensate for the lack of such disclosure, the Examiner relies relies primarily on two references, namely Ritter et al., Cancer Biology 1991 ("Ritter 1991") and Ritter et al., Immunobiology 1990 ("Ritter 1990"). However, applicants submit that neither of these references supplies what it missing from the primary reference.

Ritter 1991 discloses on page 406, column 1 two approaches for augmenting the immunogenicity of gangliosides in a mouse, and states that only one of these approaches is capable of inducing consistent IgG antibodies to gangliosides in the mouse. Ritter 1991 describes this approach as covalently attaching gangliosides to foreign carrier proteins such as KLH.

Although Ritter 1991 refers to the conjugation of GM2 to KLH, there is no description of the chemical nature of the conjugate or of how to make the conjugate. Thus, Ritter 1991 neither discloses anything conjugated through the ceramide, nor enables making any such conjugate. Applicants respectfully direct the Examiner's attention to the highlighted portion of claim 78 above relating to the conjugation, which recites "wherein in the conjugate the ganglioside derivative is conjugated to Keyhole Limpet Hemocyanin or the derivative thereof through a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative to the ε-aminolysyl group of Keyhole Limpet Hemocyanin or the derivative thereof." The Examiner's indication that one skilled in the art would interpret Ritter 1991 to involve ceramide conjugation is only speculation. Based on Ritter 1991, one skiiled in the art would not understand that the linkage would be through the ceramide. The Examiner tries to justify that the references teach linkages

through the ceramide by using Ritter 1990. However, Ritter 1990 does **not** teach conjugation in a ceramide region.

Ritter 1990 describes making chemical derivatives of GD3. The four derivatives described in Table 1 on page 34 are as follows: (1)amide, which is not immunoreactive with monoclonal antibodies to native GD3; (2) gangliosidol, which is not immunoreactive with monoclonal antibodies to native GD3; (3) lactone I, which is reactive but less than native GD3; and (4)lactone II, which is also reactive but less than native GD3. In Ritter 1990, there is no discussion of a conjugation to KLH. There is merely a description of chemical modifications of the ganglioside. Applicants point out to the Examiner that these derivatives are in the carbohydrate portion and not in the ceramide.

Based on the Table 4 in Ritter 1990, one would interpret that for GD3, the preference is to make a Lactone 1 derivative, which is a lactone chemically derivatized in the carbohydrate since it is more immunogenic than GD3 itself. Based on Ritter 1990, one would probably make a Lactone derivative. However, there is no suggestion of using the ceramide for such derivative.

The Examiner's attempt to use Ritter 1990 to support his obviousness speculation is incorrect because: (1) Ritter 1990 discloses that the conjugation is through the carbohydrate, not the ceramide; and (2) Ritter 1990 teaches away from ceramide conjugation and indicates that conjugation through a lactone is preferred.

Thus, there is neither a specific disclosure, nor is it obvious

from either Ritter 1990 or Ritter 1991 to conjugate through the ceramide. Accordingly, the primary reference (i.e. Livingston et al.) in view of Ritter 1990 and Ritter 1991 does not teach, suggest or disclose the claimed invention Moreover, the other cited references do not supply what is missing from either the primary reference, Ritter 1990 or Ritter 1991.

The Examiner cited Uemura et al as disclosing that ozonolysis and reduction of various sphingolipids do not affect the haptenic activity with antibodies. The Examiner stated that the combination [of references] provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. However, Uemura et al does not supply what is missing from the primary reference with respect to conjugation through a ceramide-derived carbon to a carrier protein.

The Examiner cited Kensil and Marciani for their disclosures with respect to QS-21. The Examiner cited Livingston et al. (U.S. Patent No. 5,102,663) with respect to various gangliosides being cell membrane components of melanoma. Accordingly, neither of these references disclose what is missing from the primary reference with respect to conjugation through a ceramide-derived carbon to a carrier protein.

The Examiner cited Liane et al (Journal of Biological Chemistry), alleging that it "teaches a method for covalent coupling of gangliosides to amino ethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the spingosine moiety (i.e. the instant carbon double bond of ceramide)

and coupling of the carboxyl bearing product to the amino group bearing glass beads." Applicants submit that Liane does not supply what is missing from the primary reference with respect to conjugation through a ceramide-derived carbon. In support, applicants attach hereto as **Exhibit B** a copy of Helling et al., Cancer Research 54: 197-203, which was cited as reference 3 in an information disclosure statement filed on May 2, 1997 in connection with the subject application. Applicants point out that Helling et al. addresses the cited reference (i.e. Liane et al.) on page 201, second paragraph of the discussion stating the "earlier" Liane et al. method

> is of limited use for the conjugation of gangliosides to carrier proteins because it requires acetylated, methyl ester derivatives of gangliosides to avoid coupling via the sialic acid carboxyl group. Deacylation after conjugation under basic conditions is necessary, conditions most proteins cannot be exposed to without degradation.

Applicants point out that the claimed invention recites in part "...a conjugate of i) a ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising a sphingosine base, to ii) **Keyhole Limpet Hemocyanin** or a derivative thereof comprising an ε-aminolysyl group..." [emphasis added]. Keyhole Limpet Hemocyanin is a carrier protein and accordingly, the Liane et al. methods would not enable a conjugation such as that recited in the claims because the Liane et al. conditions would result in protein degradation. Accordingly Liane et al. does not provide what is missing from the primary reference, i.e. a teaching of a conjugation of a ganglioside to a protein through a ceramide derived carbon, and an enabling disclosure of how to do so. Therefore, the primary reference in

view of Liane et al. does not teach, suggest or disclose the claimed invention.

Accordingly, the primary reference, i.e. Livingston 1989 in view of the other cited references, namely Ritter 1990, Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter 1991, Kensil et al. (The Journal of Immunology), and Marciani et al. (Vaccine) and Uemura et al (J Biochem) does not render obvious the applicants' claimed invention. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claim 114 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem) as applied to claims 69-81 and 83-96 above and further in view of Irie et al. (U.S. Patent Nol 4,557,931) for reasons made of record for claim 68 in Paper No. 23, 10-5-99. The Examiner stated that applicants' arguments have been carefully considered but are not persuasive. Applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation of the ganglioside derivative through a ceramide derived carbon. The Examiner stated that this is not persuasive, the conjugation procedure as combined provides for the identical procedure as applicants' coupling procedure. The Examiner stated moreover, the combination provides a reasonable expectation of

success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the heptenic reactivity with antibodies. The Examiner stated Applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the prior art would not arrived at the claimed product and methods. The Examiner stated Applicants' arguments are not persuasive and the rejection stands across the new claims.

In response, applicants respectfully traverse the Examiner's above rejection for the reasons stated above supra on pages 11-17. Applicants contend that Irie does not supply what is missing from either the primary reference or any of the other references, i.e. with respect to conjugation of gangliosides through a ceramide-derived carbon to carrier proteins. Accordingly Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem) as applied to claims 69-81 and 83-96 above and further in view of Irie et al. (U.S. Patent No. 4,557,931) does not teach, suggest or disclose applicants' claimed invention and therefore do not render obvious the claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 78-93 and 95-100.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

7-27-01

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